APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline

Ondine van de Rest, PhD
Yamin Wang, MPH
Lisa L. Barnes, PhD
Christine Tangney, PhD
David A. Bennett, MD
Martha Clare Morris, ScD

Correspondence to
Dr. van de Rest:
Ondine.vandeRest@wur.nl

ABSTRACT

Objective: To examine the association between consumption of seafood and long-chain n-3 fatty acids with change in 5 cognitive domains over an average of 4.9 years.

Methods: From an ongoing longitudinal, community-based epidemiologic study of aging and dementia (the Rush Memory and Aging Project), we included 915 participants (age 81.4 ± 7.2 years, 25% men) who had completed at least one follow-up cognitive assessment and dietary data. Diet was assessed by semiquantitative food frequency questionnaire. Scores for global cognitive function and 5 cognitive domains (episodic, semantic, and working memory, perceptual speed, and visuospatial ability) were assessed using 19 cognitive tests. Mixed models adjusted for multiple risk factors of cognitive change were used to assess the associations.

Results: Consumption of seafood was associated with slower decline in semantic memory (β = 0.024; $p = 0.03$) and perceptual speed (β = 0.020; $p = 0.05$) in separate models adjusted for age, sex, education, participation in cognitive activities, physical activity, alcohol consumption, smoking, and total energy intake. In secondary analyses, *APOE* ε4 carriers demonstrated slower rates of decline in global cognition and in multiple cognitive domains with weekly seafood consumption and with moderate to high long-chain n-3 fatty acid intake from food. These associations were not present in *APOE* ε4 noncarriers. Higher intake levels of α-linolenic acid were associated with slower global cognitive decline, but also only in *APOE* ε4 carriers.

Conclusions: These results suggest protective relations of one meal per week of seafood and long-chain n-3 fatty acids against decline in multiple cognitive domains. The role of *APOE* ε4 in this association needs further study. ***Neurology*® 2016;86:2063–2070**

GLOSSARY

ALA = α-linolenic acid; **DHA** = docosahexaenoic acid; **EPA** = eicosapentaenoic acid; **FFQ** = food frequency questionnaire; **MAP** = Rush Memory and Aging Project; **SU** = standardized units.

The primary structural component of the brain is the long-chain n-3 fatty acid, docosahexaenoic acid (DHA) (22:6 n-3), of which the direct nutrient source is seafood. DHA is also metabolized in vivo from the n-3 fatty acids eicosapentaenoic acid (EPA) (20:5 n-3) and α-linolenic acid (ALA) (18:3 n-3). The importance of seafood and n-3 fatty acids in the prevention of dementia has been demonstrated through a number of prospective epidemiologic studies,[1,2] most of which reported findings for global cognitive functioning. Few examined associations with specific cognitive domains that may provide clues to the underlying biologic mechanisms of effect. Further, we are not aware of a previous study investigating whether APOE, the gene encoding the lipid protein responsible for intercellular trafficking of cholesterol and other lipids involved in brain composition and functioning,[3] and more specifically the APOE ε4 genotype, a major risk factor for dementia,[4] might modify the relations of seafood/n-3 fatty acid intake to domain-specific cognitive decline. We investigated whether APOE ε4 modifies the association between seafood and n-3 fatty acid intakes and domain-specific cognitive decline in a community-based, prospective study.

Supplemental data at Neurology.org

From the Division of Human Nutrition (O.v.d.R.), Wageningen University, the Netherlands; and Department of Internal Medicine, Section on Nutrition and Nutritional Epidemiology (Y.W., M.C.M.), Rush Alzheimer's Disease Center (L.L.B., D.A.B.), Department of Behavioral Sciences (L.L.B.), Department of Clinical Nutrition (C.T.), and Department of Neurology (D.A.B.), Rush University Medical Center, Chicago, IL.

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METHODS

Study population. Participants are from the Rush Memory and Aging Project (MAP), an ongoing longitudinal, community-based study of aging and dementia.[5] They were recruited from more than 40 retirement and subsidized housing communities across northeastern Illinois, in addition to church groups and social service agencies. Participants were free of known dementia at enrollment into the study and agreed to annual clinical evaluation. From February 2004 to 2013, the MAP study participants were invited to complete food frequency questionnaires. During that period, there were 1,306 active participants, 1,068 of whom completed the dietary questionnaire, and 960 survived and completed at least one follow-up cognitive assessment for the analyses of change in cognition. Of these, 915 had nonmissing data on n-3 fatty acid dietary components.

Standard protocol approvals, registrations, and patient consents. The Institutional Review Board of Rush University Medical Center approved this study and all participants signed written informed consent.

Dietary assessment. Dietary intake was assessed by a semiquantitative food frequency questionnaire (FFQ) that was validated for use in a population-based study of older community residents.[6] Participants were asked to report usual frequency of intake of 144 food items over the previous 12 months. Nutrient levels and total energy for each food item were based either on natural portion sizes (e.g., slice of bread) or according to age- and sex-specific portion sizes from national dietary surveys. The FFQ included 4 seafood items: tunafish sandwich, fish sticks/fish cakes/fish sandwich, fresh fish as a main dish, and shrimp/lobster/crab. The use of fish oil supplements was also ascertained. Weekly consumption of seafood was computed by summing the responses to the 4 seafood items. Intakes of n-3 fatty acids were obtained by multiplying the nutrient content of individual food items by the frequency of consumption and summing over all items. For these analyses, we investigated dietary intakes of the long-chain n-3 fatty acids, EPA (20:5 n-3), DHA (22:6 n-3), and ALA (18:3 n-3), a long-chain n-3 fatty acid that can be consumed through plant sources. Nutrient intakes were energy-adjusted by the regression residual method.[7]

Cognitive testing. A standardized battery including 21 cognitive tests was administered at each annual evaluation, 19 of which were used to measure decline in global cognition and 5 cognitive domains: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability, as previously described.[8] For analyses, we computed composite scores of the 5 domains and of all 19 tests to measure global cognition. To compute the composite measures, raw scores on each test were first converted to z scores using the baseline mean and standard deviation for the entire cohort. The z scores were then averaged over all tests. The composite scores minimize floor and ceiling effects of the individual tests as well as other sources of measurement error. The Mini-Mental State Examination[9] was also administered for descriptive purposes.

Covariates. Model covariates were based on information current to the baseline cognitive assessment for these analyses. Age and education were modeled in years. Smoking behavior (never smoked, former smoker, or current smoker) was based on a series of questions. Alcohol consumption (grams per day) was computed from 3 questions on the FFQ about usual frequency of consumption of beer, wine, and liquor. Frequency of participation in cognitively stimulating activities was quantified with a previously established scale[8] wherein people rated (5-point scale) how often over the past year they had participated in 7 cognitive activities (reading, library visits, reading newspapers, reading magazines, reading books, writing letters, playing games). Hours of physical activity per week was based on standardized questions[10,11] that assessed the sum total of minutes spent on each of 5 activities (walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, swimming or water exercise). Presence of diabetes (self-reported history or antidiabetic medication use), hypertension (self-reported history, measured blood pressure $\geq$160 mm Hg systolic or $\geq$95 mm Hg diastolic, or current use of antihypertensive medications), heart disease (self-reported history of myocardial infarction or digitalis use), and stroke (self-reported history and neurologic examination) were modeled as dichotomous variables.

APOE genotype was determined using DNA extracted from peripheral blood lymphocytes as previously described.[12] Genotyping was performed by Agencourt Bioscience Corporation (Beverly, MA). Participants with one or more copies of the ε4 allele were considered ε4 carriers.

Statistical analysis. We used linear mixed models to examine the relations of seafood meals and n-3 fatty acid intake to change in cognitive function. Both linear and nonlinear relations of the n-3 fatty acid nutrient variables were considered by modeling the variables in tertiles and also as linear trend variables in which all participants in a tertile were coded at the median level and modeled as a categorical variable. Seafood consumption was modeled as an indicator variable of one or more (1+) seafood meals per week vs <1 (the referent category) based on findings from previous studies.[13–17] Models were adjusted for age (years), sex, education (years), frequency of participation in cognitively stimulating activities, energy intake (only for seafood models), physical activity (hours of activity per week), alcohol consumption (grams per day of beer, wine, and liquor), smoking (never/former/current), time, and time interactions with each model covariate. In a second model, we added covariates for cardiovascular risk factors (hypertension, diabetes, myocardial infarction, and stroke) that may be considered both potential mediators and confounders of the hypothesized relations. We performed tests for statistical interaction by adding to the basic model 2-way multiplicative terms between the dietary variable and *APOE* ε4 and 3-way multiplicative terms between the dietary variable, *APOE*-ε4, and time.

Because of significant interactions between intakes of seafood and n-3 fatty acids and *APOE* ε4 and time for the cognitive outcomes in the basic-adjusted models, we subsequently ran separate models within strata of *APOE* ε4 carriers and *APOE* ε4 noncarriers as secondary analyses. All analyses were performed using SAS (SAS Institute, Cary, NC) and $p \leq 0.05$ was considered significant.

RESULTS

The sample of 915 participants was followed on average 4.9 ± 2.5 years and had a mean of 5.7 cognitive assessments. Mean age of the participants at baseline was 81.4 ± 7.2 years and 25.5% were male. Compared with participants in the lowest tertile of long-chain n-3 fatty acid intake, those in the highest tertile were more likely to be male, *APOE* ε4 carriers, and physically active, and somewhat less likely to have a history of diabetes, hypertension, or stroke. They also had higher baseline scores on some of the cognitive domains (table 1). Participants in the

Table 1 Characteristics of 915 participants at baseline by energy-adjusted tertiles of long-chain (EPA + DHA) n-3 fatty acids and ALA (18:3 n-3) intake

	Long-chain n-3 fatty acids (DHA [22:6] + EPA [20:5])			ALA (n-3 18:3)		
	Tertile			Tertile		
	1	2	3	1	2	3
No.	316	304	295	302	318	295
Dietary intake, g/d, median (range)	0.02 (0–0.04)	0.07 (0.05–0.12)	0.25 (0.12–2.05)	0.75 (0.38–0.86)	0.98 (0.87–1.08)	1.22 (1.09–2.05)
Demographic variables						
Age, y, mean ± SD	81.9 ± 7.1	81.0 ± 7.5	81.3 ± 7.0	80.7 ± 7.5	81.9 ± 7.0	81.6 ± 7.1
Male, %	20	27	30	18	27	32
Education, y, mean ± SD	14.7 ± 2.9	14.8 ± 2.9	15.3 ± 2.9	14.9 ± 2.9	14.9 ± 2.9	15.0 ± 3.0
APOE ε4, %	21	21	24	21	23	22
Smoking, %						
Current	2	3	3	3	2	2
Former	39	39	39	39	39	38
Never	59	58	58	58	58	59
Alcohol, g/d, mean ± SD	4.8 ± 10.0	3.8 ± 7.6	4.6 ± 8.5	5.1 ± 9.8	4.3 ± 8.9	3.8 ± 7.3
Physical activity score,[a] h/wk, mean ± SD	3.0 ± 3.6	3.4 ± 4.1	3.6 ± 3.3	3.6 ± 3.8	3.2 ± 3.9	3.1 ± 3.2
Cognitive activities score, frequency, mean ± SD	3.2 ± 0.7	3.2 ± 0.7	3.2 ± 0.6	3.2 ± 0.7	3.2 ± 0.6	3.2 ± 0.6
Diabetes, %	14	14	12	12	14	16
Hypertension, %	76	79	74	75	75	79
Stroke, %	11	10	5	10	8	9
Myocardial infarction, %	16	18	16	15	14	21
Cognitive test score, mean ± SD						
Baseline MMSE	27.7 ± 2.6	27.8 ± 2.9	27.8 ± 2.5	27.8 ± 2.5	27.8 ± 2.6	27.8 ± 2.9
Global cognition	0.09 ± 0.58	0.13 ± 0.65	0.15 ± 0.58	0.13 ± 0.58	0.12 ± 0.62	0.11 ± 0.61
Episodic memory	0.13 ± 0.75	0.18 ± 0.77	0.16 ± 0.76	0.19 ± 0.73	0.13 ± 0.76	0.14 ± 0.79
Semantic memory	0.14 ± 0.68	0.12 ± 0.74	0.18 ± 0.61	0.17 ± 0.65	0.11 ± 0.73	0.16 ± 0.64
Working memory	0.07 ± 0.75	0.10 ± 0.80	0.11 ± 0.77	0.07 ± 0.78	0.13 ± 0.78	0.07 ± 0.75
Perceptual speed	0.04 ± 0.77	0.08 ± 0.80	0.12 ± 0.78	0.09 ± 0.80	0.09 ± 0.78	0.05 ± 0.77
Visuospatial ability	0.03 ± 0.77	0.10 ± 0.85	0.24 ± 0.75	0.04 ± 0.82	0.13 ± 0.80	0.20 ± 0.75
Dietary intake						
Seafood consumption, n (%) ≥1 meal/wk	182 (57)	270 (89)	273 (92)	220 (73)	262 (82)	243 (82)
Fish oil supplement, n (%)	52 (16)	47 (15)	62 (21)	57 (19)	59 (18)	45 (15)
Total energy intake, kcal/d, mean	1,837	1,727	1,641	1,700	1,824	1,681

Abbreviations: ALA = α-linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MMSE = Mini-mental state examination.
[a] Physical activity scores: 1 = daily; 2 = 3–4 times/wk; 3 = 1–2 times/wk; 4 = 2–3 times/mo; 5 = once a month; 6 = <1/mo; 7 = never.

highest tertile of ALA intake tended to have lower alcohol consumption and to be less physically active than participants in the lowest tertile, and were more likely to have a history of cardiovascular conditions.

Nutrient relations in the total sample. Global cognitive scores in the total sample declined on average by 0.083 standardized units per year (SU/y). When we examined the decline in rates by seafood consumption in models adjusted for age, sex, education, total caloric intake, alcohol consumption, smoking, and participation in cognitive and physical activities, those who consumed one or more seafood meals per week did not demonstrate slower decline in global cognition, but did have significantly slower rates of decline in semantic memory and perceptual speed compared with those who consumed less (table 2). These associations did not change with additional adjustment for cardiovascular risk factors (stroke, hypertension, myocardial infarction, diabetes) that could potentially

Table 2 Association of seafood consumption and dietary intake of energy-adjusted α-linolenic acid (18:3 n-3) with annual rate of change in global cognitive score and in 5 cognitive domain scores based on multiple-adjusted linear mixed models including primary confounders[a] among 915 MAP participants (2004–2013)

Model	Median no. or g/d	Global cognitive β, *p* Value	Episodic memory β, *p* Value	Semantic memory β, *p* Value	Working memory β, *p* Value	Visual spatial β, *p* Value	Perceptual speed β, *p* Value
Seafood							
<1 meal per wk	0.5	Referent	Referent	Referent	Referent	Referent	Referent
1+ meals per wk	2.0	0.018 (0.08)	0.015 (0.23)	0.024 (0.03)	0.016 (0.11)	0.011 (0.30)	0.020 (0.05)
Long-chain n-3 fatty acids							
Tertile 1	0.02	Referent	Referent	Referent	Referent	Referent	Referent
Tertile 2	0.07	0.008 (0.36)	0.011 (0.32)	0.007 (0.52)	0.009 (0.33)	0.001 (0.90)	0.008 (0.38)
Tertile 3	0.25	0.009 (0.32)	0.009 (0.45)	0.007 (0.54)	0.017 (0.10)	−0.003 (0.75)	0.010 (0.32)
p Value for linear trend		0.42	0.60	0.64	0.13	0.69	0.40
α-linolenic acid							
Tertile 1	0.75	Referent	Referent	Referent	Referent	Referent	Referent
Tertile 2	0.98	0.006 (0.49)	0.010 (0.39)	0.015 (0.18)	−0.001 (0.91)	0.014 (0.15)	0.014 (0.14)
Tertile 3	1.22	0.010 (0.30)	0.019 (0.11)	0.010 (0.39)	0.010 (0.30)	0.005 (0.63)	0.004 (0.67)
p Value for linear trend		0.30	0.11	0.38	0.31	0.61	0.66

Abbreviations: MAP = Rush Memory and Aging Project.
[a] Models adjusted for age, sex, education, participation in cognitive activities, energy intake (seafood only), physical activity, alcohol consumption, smoking, time, and time interactions with each model covariate.

mediate the relations between seafood and decline (data not shown). Dietary intakes of ALA (table 2) and food sources of the long-chain n-3 fatty acids were not associated with any measure of cognitive decline in the overall sample. However, the group of 161 fish oil supplement consumers had slower rates of decline in the global cognitive measure ($\beta = 0.024$, $p = 0.02$) and in episodic memory ($\beta = 0.027$, $p = 0.03$) compared with the nonconsumers.

Analyses by *APOE* ε4 status. We next investigated potential modifications in the associations of the nutrient variables on cognitive decline by *APOE* ε4 status. Because statistical interactions were observed among all 3 nutrient variables and multiple cognitive measures and time in the basic adjusted models, we conducted secondary analyses stratified by *APOE* ε4 status (table 3 and table e-1 on the *Neurology*® Web site at Neurology.org).

Among the 178 *APOE* ε4 carriers, the mean rate of decline in global score was −0.126 SU/y. Weekly seafood consumption in this group was associated with slower declines in global cognitive score (figure), episodic memory, semantic memory, and perceptual speed compared with less consumption (table 3). *APOE* ε4 carriers also demonstrated linear protective relations with increased intakes of long-chain n-3 fatty acids reflected as slower declines in semantic memory and perceptual speed. However, nonlinear associations for the long-chain n-3 fatty acids were observed for global cognition, episodic memory, and working memory, such that participants in the second tertile of intakes had significantly slower declines, but there were no benefits with higher intakes. The plant-based 18:3 n-3 fatty acid, ALA, had marginally linear protective relations with global cognitive score ($p = 0.05$) and perceptual speed ($p = 0.07$) in the group of *APOE* ε4 carriers.

In further analyses we investigated an intermediary role of cardiovascular conditions on the observed associations among the *APOE* ε4 carriers. The addition of covariates for stroke, myocardial infarction, diabetes, and hypertension to basic-adjusted models reduced the protective association of seafood consumption on global cognitive decline ($\beta = 0.047$, $p = 0.06$), and that with episodic memory was reduced and no longer remained ($\beta = 0.048$, $p = 0.12$). By contrast, the protective associations with semantic memory ($\beta = 0.086$, $p = 0.01$) and perceptual speed ($\beta = 0.066$, $p = 0.02$) remained. In parallel analyses of the long-chain n-3 fatty acids, the associations with cognitive decline and the second tertile of intakes changed little and remained significant. The exception was working memory, for which there was a 32% diminution in the estimated effect that was no longer significant. ($\beta = 0.046$, $p = 0.11$). The marginal associations for ALA intake were further weakened after the adjustments for cardiovascular

Table 3 Association of seafood and of energy-adjusted long-chain (EPA + DHA) n-3 fatty acids and ALA (18:3 n-3) with annual rate of change in global cognitive score and in 5 cognitive domain scores among 178 MAP participants who were *APOE* ε4-positive based on multiple-adjusted linear mixed models[a] (2004–2013)

Model	Median no. or g/d	Global cognitive β (*p* Value)	Episodic memory β (*p* Value)	Semantic memory β (*p* Value)	Working memory β (*p* Value)	Visual spatial β (*p* Value)	Perceptual speed β (*p* Value)
Seafood meals							
<1/wk	0.5	Referent	Referent	Referent	Referent	Referent	Referent
1 + wk	2.0	0.058 (0.01)	0.062 (0.03)	0.091 (0.003)	0.016 (0.55)	0.027 (0.30)	0.072 (0.005)
Long-chain n-3 fatty acids							
Tertile 1	0.02	Referent	Referent	Referent	Referent	Referent	Referent
Tertile 2	0.07	0.073 (0.002)	0.064 (0.03)	0.079 (0.01)	0.068 (0.01)	0.045 (0.10)	0.061 (0.02)
Tertile 3	0.27	0.046 (0.04)	0.031 (0.27)	0.076 (0.01)	0.032 (0.21)	0.019 (0.46)	0.062 (0.01)
p Value for linear trend		0.26	0.63	0.06	0.59	0.77	0.05
ALA							
Tertile 1	0.76	Referent	Referent	Referent	Referent	Referent	Referent
Tertile 2	0.99	0.028 (0.25)	0.012 (0.69)	0.042 (0.19)	0.022 (0.43)	0.021 (0.45)	0.047 (0.08)
Tertile 3	1.22	0.048 (0.05)	0.049 (0.11)	0.052 (0.11)	0.038 (0.17)	0.017 (0.54)	0.049 (0.07)
p Value for linear trend		0.05	0.11	0.11	0.16	0.53	0.07

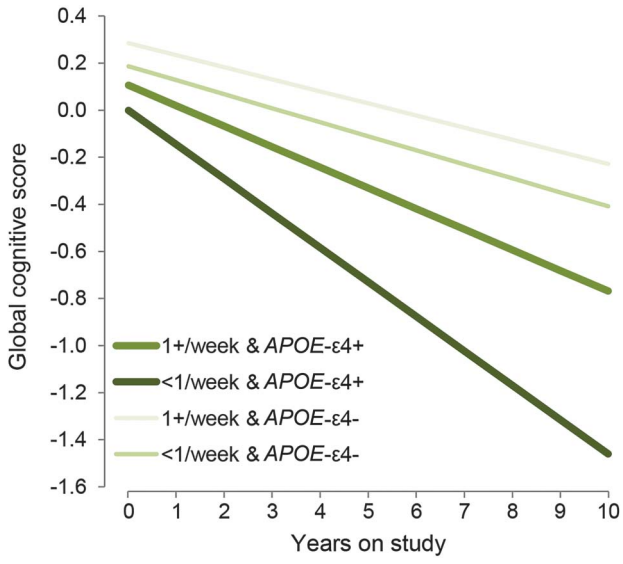
Abbreviations: ALA = α-linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MAP = Rush Memory and Aging Project.
[a] Models adjusted for age, sex, education, participation in cognitive activities, energy intake (seafood only), physical activity, alcohol consumption, smoking, time, and time interactions with each model covariate.

conditions (global cognition β = 0.089, $p = 0.10$; perceptual speed β = 0.107, $p = 0.08$).

To investigate the extent to which the findings could be explained by dietary changes or to invalid reporting among individuals with ongoing disease processes, we reanalyzed the data after eliminating those in the lowest 10% of baseline cognitive scores. There were no appreciable changes in the estimated effects of the second tertile of long-chain n-3 fatty acid intake for any cognitive measure except for a marginal association for episodic memory (β = 0.054, $p = 0.07$). For seafood consumption, only the association for semantic memory remained (β = 0.049, $p = 0.03$) and the previously observed associations for ALA no longer lasted (all $p > 0.15$).

In *APOE* ε4 noncarriers, the average decline in global cognitive score was −0.078 SU/y. There was no evidence of association for any of the nutrient exposures and cognitive measures. (table e-1) Further, there was no evidence of statistical interaction between fish oil supplement use and *APOE* ε4 on cognitive decline.

Figure Association of seafood consumption with rate of change in global cognitive score among *APOE* ε4-positive and *APOE* ε4-negative participants



Association of <1 seafood meal per week and 1 or more seafood meals per week with annual rate of change in global cognitive score among 178 Rush Memory and Aging Project (MAP) participants who were *APOE* ε4-positive and among 632 MAP participants who were *APOE* ε4-negative based on multiple-adjusted linear mixed models, 2004–2013.

DISCUSSION The present study is one of a few that investigated associations between seafood and long-chain n-3 fatty acid intake with change in cognitive domains. Our findings support the hypothesis that consumption of seafood and long-chain n-3 fatty acids reduces age-related decline in multiple cognitive domains. The study findings suggest that the relation may be more pronounced in individuals who have the *APOE* ε4 genotype.

APOE ε4 is associated with increased brain neuroinflammation and deposition of Aβ in senile plaques.[18]

DHA is a major polyunsaturated fatty acid in the brain that is obtained through diet and has potent anti-inflammatory and antioxidative properties that have been demonstrated in some brain animal models.[19] One such study of *APOE* ε4 and *APOE* ε3 targeted replacement mice found that the phenotypic deleterious effects of *APOE* ε4 on cognition and brain neuropathology were prevented by a DHA-rich diet.[20]

Our associations of higher dietary n-3 fatty acids with slower cognitive decline among *APOE* ε4 carriers are in accordance with a prior observational study showing associations in *APOE* ε4 carriers between higher plasma EPA and DHA and slower decline in visual working memory.[21] Yet several other observational studies reported associations of higher fish consumption or erythrocyte levels of EPA/DHA with dementia in noncarriers of *APOE* ε4.[22–24] However, the interaction terms in these studies were not significant at $p \leq 0.05$, inconsistent per outcome measure, or based on very small numbers, so the evidence restricting the association to *APOE* ε4 noncarriers is not strong. The robustness of the current associations is reinforced by our findings in a subsample of deceased participants with autopsy data, in which we recently showed associations between higher seafood consumption with lower levels of Alzheimer disease neuropathology also in *APOE* ε4 carriers only.[25] A very recent study observed associations between fish oil supplement use and less cognitive decline and less brain atrophy in the entire study cohort that, after stratification, remained significant in the *APOE* ε4 noncarriers only.[26] Results from randomized placebo-controlled intervention trials are also mixed, observing positive effects of long-chain n-3 fatty acids among *APOE* ε4 carriers[27,28] or in *APOE* ε4 noncarriers.[29] One possible explanation for the previous findings of association among *APOE* ε4 noncarriers is the larger number of participants being *APOE* ε4 noncarriers. Our contrasting result with the majority of previous observational and intervention studies may also be due to the relatively older study sample (mean age at baseline was 81.4 years), or could also be a chance finding. The interaction between *APOE* ε4 status and long-chain n-3 fatty acid intake is not fully understood. It has been suggested that *APOE* ε4 carriers may have compromised brain reserves or poor brain protection and repair mechanisms, making them more vulnerable to detrimental factors, but also to beneficial factors, such as long-chain n-3 fatty acid intake.[30] It has also been proposed that EPA and DHA may help to compensate brain glucose hypometabolism.[31] Alternately, it has also been hypothesized that *APOE* ε4 carriers may modulate n-3 fatty acid metabolism.[32]

A number of studies have reported protective associations of seafood intake on slower global cognitive decline.[17,33–35] Most observed protective benefits at the level of one seafood meal per week, which is consistent with our findings. In addition, our finding of slower decline (in *APOE* ε4 carriers) among persons in the second tertile of long-chain n-3 fatty acid intake (range 0.35–0.84 g/wk) also approximates the DHA/EPA content of one 3-oz serving of seafood per week (e.g., shrimp, 0.23 g; pollock, 0.43 g; sockeye salmon, 1.04 g; bluefin tuna, 1.28 g). To illustrate the relevance of our findings, we compared the mixed model effect estimates for age over time on global cognition $\beta = -0.004$ to that for weekly seafood consumption ($\beta = 0.058$). Based on the comparison of these effect estimates, the rate of cognitive decline among weekly seafood consumers was the equivalent of being 14.5 years younger in age.

Our findings of associations with multiple cognitive domains are supported by previous prospective studies that found associations of higher concentrations of n-3 fatty acids measured in diet or plasma with slower declines in perceptual speed,[33] semantic memory,[35] verbal memory,[36] and verbal fluency.[37,38] Together, the findings that n-3 fatty acids are associated with multiple cognitive domains involving multiple brain regions and cognitive systems suggest that they may play a fundamental role in brain neuroprotection.

There are many strengths of the study that lend confidence in the overall findings. The prospective design and annual cognitive assessments using a comprehensive battery of tests over 2–10 years allowed for more precise measurement of individual cognitive trajectories to test dietary associations. This precision was also provided by the use of multiple tests to measure specific cognitive domains. The relatively long follow-up period (mean of 4.9 years) after the dietary assessment reduced the potential for bias due to dietary changes caused by underlying diseases or cognitive changes. Further, the results for n-3 fatty acid intake remained after exclusion of the lowest (10%) baseline cognitive scores, i.e., those with poorer cognition, which could have impaired recall on the FFQ. Whereas dietary intake was assessed with a FFQ that was validated in a community sample of older Chicago residents,[6,39] there was likely error in the measurement of n-3 fatty acid intake due to nonspecific information obtained on the type of fresh fish consumed as a main dish. This type of measurement error would tend to bias the results toward the null and thus likely had minimal influence on the study findings. As with all observational studies, despite adjustment for the most relevant potential confounders, residual confounding is still possible. Another limitation of the study is the relatively small sample size to detect modest associations within

subgroups. Therefore, it is possible that a protective relation of n-3 fatty acids on cognitive decline also exists among *APOE* ε4 noncarriers, but the power of the study was insufficient to detect an association. The average rate of cognitive decline in this group was substantially less (−0.078) than the rate in the *APOE* ε4 carriers (−0.126).

Loss in cognitive abilities and dementia are among the most feared and debilitating conditions of aging and currently there are no effective treatments. The role of seafood consumption may be differential depending on *APOE* ε4 status. Randomized trials would be required to further clarify this possible distinction. Dietary behaviors, such as the consumption of one seafood meal per week, are relatively simple measures for individuals to take with few negative consequences and potentially many established health benefits, if not cognitive.[40]

Comment: Gene-environment interactions in dementia—Not just another fish story

Many observational studies have shown relationships between dietary omega-3 fatty acids and cognitive outcomes, but relatively few have examined gene–environment interactions due to *APOE* genotype. In this study, van de Rest et al.[1] highlight the modifying effect of *APOE* genotype on cognitive effects of dietary omega-3 fatty acids, finding "protective" effects of dietary seafood/omega-3s only in the ε4 carrier group, which is at higher risk of Alzheimer disease. Prior observational studies that have incorporated *APOE* genotype have reported mixed results, sometimes concluding that the omega-3 benefit is stronger in the ε4 carriers and sometimes in the ε4 noncarriers. The finding in the present study is strengthened by a recent report from the same group showing an inverse relationship between dietary omega-3 and autopsy-confirmed Alzheimer disease brain pathology, also only in ε4 carriers.[2] However, observational studies and clinicopathologic studies cannot determine with certainty whether dietary or supplemental omega-3s will attenuate cognitive decline in individuals at risk. Randomized, placebo-controlled trials are necessary to definitively answer this question. While most of these have been negative,[3] few have included *APOE* stratification in the analyses, so may have failed to appreciate genotype-specific effects of omega-3 supplementation.

The implications of the Morris study for practice or for public health are modest at present. Since the amount of seafood that was "protective" in this study was the equivalent of one seafood meal per week, and since the American Stroke Association guidelines already recommend eating fish twice a week for vascular health, even the most optimistic view of this study would not justify a change in a neurologist's dietary recommendation. Furthermore, since the literature remains mixed regarding *APOE* and omega-3s, it is premature to suggest *APOE* genotyping as a tool to guide dietary recommendations.

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Joseph Quinn, MD

From the Department of Neurology, Oregon Health and Science University, Portland VA Medical Center, OR.

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AUTHOR CONTRIBUTIONS

O.v.d.R. commissioned the statistical analyses and drafted the manuscript. Y.W. performed the statistical analyses. M.C.M. supervised the data analysis and interpretation. All authors critically reviewed the manuscript and approved the final draft.

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